AF/JDW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Chang-Yi LIN et al.	Confirmation No: 9676
Appl. No.	: 10/800,622	
Filed	: March 16, 2004	
Title	: STABLE AND TASTE MASKED PHARMACEUTICAL DOSAGE FORM USING POROUS APATITE GRAINS	
TC/A.U.	: 1618	
Examiner	: N.G. Ebrahim	
Docket No.:	: LINC3186CIP/REF	
Customer No:	: 23364	

37 CFR §41.37 APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This brief on appeal for this application is submitted without the required appeal fee set forth in §41.20(b)(2) of $540 which has been previously submitted. Any additional fees necessary for this appeal may be charged to Deposit Account No. 02-0200. The brief is due February 28, 2010 and is timely filed.

41.37 (c)(1)(I) REAL PARTY IN INTEREST

The real party in interest is the Assignee of record, NANOTREND INO-TECH INC

41.37 (c)(1)(ii) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences with respect to the claimed invention which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal known to appellant, appellant's legal representative or assignee.

41.37 (c)(1)(iii) STATUS OF THE CLAIMS

This application contains claims 1-72. Claims 17 and 21-71 have been canceled from the application without prejudice or disclaimer and are no longer pending. Claims 1-16, 18-20 and 72 are pending and are the claims on appeal. Claims 1-16, 18-20 and 72 stand finally rejected under 35 U.S.C. 103(a) as obvious over the prior art cited and applied in the Final Rejection. However, claim 16 has not been included in any statement of rejection although it is not indicated to be allowable. Clarification of the status of this claim and the applicable rejection is requested as is time for Applicants to consider the basis of the rejection and respond thereto, with amendment, if necessary.

41.37 (c)(1)(iv) STATUS OF AMENDMENTS AFTER FINAL REJECTION

No amendment was filed after Final Rejection. A Notice of Appeal was filed in response to the Final Rejection.

41.37 (c)(1)(v) SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 relates to a stable and taste masked pharmaceutical dosage form comprising porous apatite grains and a drug entrapped in pores of said grains, wherein said grains have a size of 0.1-1000 μm and said pores of said grains have an opening of 0.5-300 nm, (page 3, lines 8-12) and the dosage form further comprising a biocompatible polymer, wherein said porous apatite grains are bound by said biocompatible polymer to form a microspherical composite having a size of 0.5-1000 μm. (Page 4, lines 14-16.)

Claim 2 further includes a water soluble polymer entrapped in pores of the grains of the porous apatite in an amount of 0.1-10% based on the weight of the grains as set forth on page 3, lines 18 and19.

Claim 12 further defines the dosage form wherein the apatite grains contain carbonate in an amount of 0.1-40% based on the weight of the grains as noted on page 10, lines 5-12 and original claim 12 and claim 13, wherein the apatite grains have a Ca to P molar ratio of 1.3 to 1.60, page 3, lines 25-26. Claim 16 provides for that the drug is zinc gluconate, copper gluconate, aspirin, ibuprophen or ascorbic acid, page 4, lines 11-12.

41.37 (c)(1)(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

THE OBVIOUSNESS REJECTIONS

A. The first obviousness rejection to be reviewed is whether claims 1-11, 13-15, 18-20 and 72 are prima facie obvious under 35 U.S.C. 103(a) as being unpatentable over Tsuru et al EP 376331 (Tsuru) in view of Lee et al (WO 0015194) and further in view of Isobe et al.

B. The second obviousness rejection to be reviewed is whether claim 12 is prima facie obvious under 35 U.S.C 103 (a) over Tsuru et al in view of Lee et al and further in view of Makoto et al.

41.37 (c)(1)(viii) ARGUMENT

THE OBVIOUSNESS REJECTIONS

Examples Of Basic Requirements of a Prima Facies Case of Obviousness

The appellant submits that the criteria set forth in the MPEP provides guidance in determining the issue of obviousness of the claims on appeal.

---SECTION---2143 Examples Of Basic Requirements of a Prima Facie Case of Obviousness

The Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. (Emphasis added.)

SECTION---2143.03 All Claim Limitations Must Be Taught or Suggested

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Appellants also most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-130) wherein it is stated that Office personnel should consider all rebuttal argument and evidence present by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

THE FIRST OBVIOUSNESS REJECTION

A. The first obvious rejection to be reviewed is of claims 1-11, 13-15, 18-20 and 72 as obvious under 35 U.S.C. 103(a) as being unpatentable over Tsuru et al EP 376331 (Tsuru) in view of Lee et al (WO0015194) and further in view of Isobe et al.

At the outset, it is to be emphasized that in evaluating the presently claimed "pharmaceutical dosage form", the shape and size of the dosage form are important in addition to the structure of the dosage form in the field related to the present invention. The problems to be solved by the inventors of the present invention are how to develop a dosage form carrying a drug which can be taken by the patients orally with the taste of the drug being masked and can be stored stably. This should be borne in mind as it is part of the invention as a whole which needs to be evaluated in determining patentability under 35 U.S.C. 103(a).

Tsuru describes slow release granules of Calcium Phosphate compounds

It is urged in the Final Rejection that Tsuru teaches drug delivery granules comprising porous granules of a calcium phosphate compound having a ratio of Ca to P of 1.3 to 1.8 (examples disclose a ratio of 1.67, and 1.5). A porosity of 0.1 to 70%, a specific surface area delivery granules comprising porous granules of a calcium phosphate compound having a ratio of Ca to P of 1.3 to 1.8 (examples disclose a ratio of 1.67, and 1.5). A porosity of 0.1 to 70%, a specific surface area of 0.1 to 50 m^2/g and a pore size of 1nm to 10 microns (abstract, page 3, lines 31-40 for preferable ratios and surface areas, and see also examples). The invention includes different types of drugs such as carcinostatics, antibiotics and the like (page 4, lines 56+).

The Tsuru reference relates to calcium phosphate compounds in general, and notes apatites, which are specific types of calcium phosphate compounds as would be appreciated by one of ordinary skill in the art. This is clearly stated on page 3, lines 15-17 of the reference noting such other compounds as tricalcium phosphates and tetracalcium phosphates to name others. Hydroxyapatite is referred to at page 5 which has a Ca/P of 1.67 which is outside of the range of 1.3 to 1.6 of claim 11 on appeal. One of ordinary skill in the art would recognize that when an apatite is used, as opposed to tricalcium phosphate or tetracalcium phosphate, in accordance with

Tsuru, the Ca/P ratio would be outside of the presently claimed range. This represents a clear teaching away from this range which is a claim limitation which cannot be ignored. Note that the claims on appeal are limited to apatites and not to the other forms of calcium phosphate referred to in the reference as would be appreciated by one of ordinary skill in the art. Moreover, the oral dosages of the present invention are not suggested by the reference as noted in the sentence bridging pages 4 and 5 of the reference in the discussion of local injection, or implantation and transvascular chemotheraphy as would be appreciated by one of ordinary skill in the art. Masking the taste is not an objective in these types of formulation. None of this suggests the presently claimed invention which is unobvious over the combination of references relied upon in the rejection.

Tsuru does not teach drugs within the pores of apatite

Applicants most respectfully submit that the conclusion with respect to the teaching of Tsuru stated in the paragraph bridging pages 3 and 4 of the Final Rejection is incorrect. Specially, it is stated that, "The granules are impregnated in the ADR solution to obtain drugs contained in the pores with the acryl polymer beads (example 6)." As would be appreciated by one of ordinary skill in the art, there is no acryl present after firing. In this regard, please note the first full paragraph of page 4 of the reference which states that the porous granules of the present invention may have a hollow structure in which the drug component is contained. The hollow granular may be produced by forming a porous coating of the calcium phosphate compound around particles of a combustible substance and heating and removing the combustible substance in a process of the firing.

As would be appreciated by one of ordinary skill in the art, this is the exact procedure described in Example 6 where the hydroxyapatite powder is coated on acryl beads (more than 50 times larger than the hydroxyapatite powder) which are then fired at 900 degrees C to form hollow granules of hydroxyapatite. There is no

indication that acryl is present, because it is not, as would be appreciated by one skill in the art. Thus, one of ordinary skill in the art would appreciate that the further statement on page 4 of the Final Rejection that Tsuru teaches that the drug and polymers are entrapped in the pores of the apatite is not correct and is most respectfully traversed. It is the firing (sintering) which binds the hydroxyapatite powder into the porous hollow granules which is consistent with the statement in the Final Rejection that Tsuru did not disclose binding of the granules into composites using a bicompatible polymer. It is the pores between the fused powder which retain the drug and not the pores of the apatite grains in accordance with the claimed invention.

In the first full paragraph on page 4 of the Final Rejection, regarding the amount of polymer and/or the amount of drug loaded, it is stated that since Tsuru teaches that the drug and polymers are entrapped in the pores of the apatites.... This aspect of the statement is traversed. It is the granules which are impregnated with the drug not the apatite grains in accordance with the present invention.

Lee does not overcome the deficiencies of the primary reference

The teachings of the Lee reference do not overcome the deficiencies with respect to the primary reference and that is stated on page 4 of the final rejection, Tsuru did not disclose binding of the granules into a composite using a biocompatible polymer. As would be appreciated by one of ordinary skill in the art, Tsuru teaches that the apatite powder is held in position by the acryl bead and then sintered to burn out the acryl and sinter the powder to form the granules. Lee teaches a calcium phosphate delivery vehicle and adjuvant. An amorphous calcium phosphate adjuvant is disclosed as noted in the summary of the invention on page 4 of the reference. Adjuvant refers to any substance that is capable of producing or enhancing a host response towards a specific active agent.

As stated on page 7 of the reference, the characteristics of the calcium-containing adjuvant includes any calcium compound although calcium phosphates and calcium sulfates are preferred. Amorphous and poorly crystalline apatitic calcium phosphates are particularly preferred. Useful calcium adjuvants include, but are not limited to calcium sulfates and calcium phosphates such as amorphous calcium phosphates, poorly crystalline apatitic calcium phosphates, dicalcium phosphate dihydrate, tricalcium phosphates, tetracalcium phosphate, monetite, monocalcium phosphate. Hydroxyapatites are included in this group. But there is absolutely no teaching which suggests using a biocompatible polymer to bind the apatite grains to form a microspherical composite having a size of 0.5 -1000 microns.

In the paragraph bridging pages 20 and 21 of the Lee reference, liposomes and polymers, particularly biodegradable polymers, are said to also increase adjuvant activity by themselves serving as a delivery vehicle for the inventive calcium phosphate adjuvant. In a preferred embodiment, a liposome or polymer will encapsulate the calcium phosphate adjuvant producing microspheres. However, this is distinctly different as would be appreciated by one of ordinary skill in the art from using a biocompatible polymer to bind the grains to form a microsphere in accordance with the presently claimed invention. Clearly, the combination of Tsuru and Lee does not render obvious the presently claimed invention and therefore it is requested that this rejection be withdrawn or reversed by the Board of Appeals.

<u>The rejection of claims 2, 8, and 9 does not stand or fall with the rejection of claims 1, 3-7, 10-11, 13, -15, 18-20 and 72</u>

The rejection of claims 2, 8-9 do not stand or fall with the rejection of claims 1, 3-7, 10-11, 13, -15, 18-20 and 72 as these claims contain an additional limitation that the pharmaceutical dosage form further comprises a water soluble polymer entrapped in pores of said grains which as noted on page 5 of the final rejection,

both the Tsuru and Lee references do not teach the use of soluble polymers disclosed in instant claim 9 which are entrapped in the pores with the active agent. Claim 9 is dependent upon claim 8, which is dependent upon claim 2, which is the first claim that introduces water soluble polymers entrapped in the pores. However, there is absolutely no suggestion of this aspect of the invention contained in the Isobe reference. The discussion of this reference contains no reference to any particular portion of the patent for the teachings discussed in the rejection. However, it appears that the portion of the reference being relied upon is in column 6 starting at line 6 for the discussion that in order to mask the taste and improve the palatability, the edible organic acid or salt thereof, especially the powdery or granule edible organic acid or a salt thereof may be coated, and the solid preparation may be a sugar coated solid preparation or a solid preparation (e.g., tablet) coated with a coating base. The examples of the coating base include gelatin, hydroxypropylmethylcelluose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose and indicated at the top of page 6 of the final rejection. However, there is nothing in the reference to suggest that the water soluble polymer is entrapped in pores of the grains, but it is coated thereon. There is no suggestion of the claim limitations of the claims on appeal in this reference nor does the combination of references render the presently claimed invention obvious. Accordingly, this rejection should be withdrawn or reversed on appeal.

The rejection of claim 13 does not stand or fall with the remaining rejected claims over the combination of Tsuru et al in view of Lee and further in view of Isobe et al.

Claim 13 depends upon claim 12 which is not included in the rejection and claim 12 contains carbonate in the apatite grains which is not suggested by the prior art relied upon in this rejection. Claim 12 is not included in the rejection as it was

subject to a further rejection with the additional reference of Makoto et al. Accordingly, this rejection should be withdrawn or reversed on Appeal.

THE SECOND OBVIOUSNESS REJECTION

B. The second obvious rejection to be reviewed is of claim 12 under 35 U.S.C. 103 (a) as being unpatentable over Tsuru et al in view of Lee et al and further in view of Makoto et al.

Claim 12 provides that the apatite grains contain carbonate in the amount of 0.1 - 40% based on the weight of the grains. As admitted on page 7 of the final rejection, neither of the references teaches the amount of carbonate in the apatite. The Makoto reference is relied upon for this teaching in this regard, the Examiner's attention is directed to page 10 of Applicant's specification, lines 17-20 wherein it is indicated that seed carbonate bands suggest that the apatite obtained in this composition is AB-type carbonated apatite. Increasing carbonate concentrations suggest sufficient amounts of carbonated ions being incorporated into the apatite lattice.

On the contrary, Otsuka which is the author's last name and Makoto, his first, on page 444 under Materials and Method teaches that tetracalcium phosphate (TTCP) and dicalcium phosphate dihydrate (DCPD) and 0 - 40% (HAP) which is hydroxyapatite seed crystals with various amounts of sodium bicarbonate as summarized in table 1. The cement powder was mixed to form this cement. In the results and discussion portion on page 446, it is stated that the X-ray diffraction profiles suggest that IMC and sodium bicarbonate did not interfere with the cement setting but apatite formation was deleted by the presence of sodium bicarbonate. Note also the presence of tetracalcium phosphate. It is most respectfully submitted

that one of ordinary skill in the art would not find this teaching to a multi-component cement to suggest, as urged in the final rejection, that Otsuka et al teaches the inclusion within the apatite grains of carbonate as required by claim 12 on appeal. Especially when combining the teachings of this reference with the teachings of the Tsuru reference for the reasons discussed above. Accordingly, it is most respectfully requested that this rejection be withdrawn or reversed on Appeal.

IX. CONCLUSION

In view of the above arguments, all of the rejections of the claims on appeal should be reversed. The application should be passed to issue.

Respectfully submitted,

BACON & THOMAS, PLLC

By: Richard E. Fichter
Richard E. Fichter
Registration No. 26,382

625 Slaters Lane - 4th Fl.
Alexandria, Virginia 22314
Phone: (703) 683-0500

REF:ref
Appeal Brief2Final.wpd

February 23, 2010

41.37 (c)(1)(viii) Claims appendix

1. A stable and taste masked pharmaceutical dosage form comprising porous apatite grains and a drug entrapped in pores of said grains, wherein said grains have a size of 0.1-1000 μm and said pores of said grains have an opening of 0.5-300 nm, and said dosage form further comprising a biocompatible polymer, wherein said porous apatite grains are bound by said biocompatible polymer to form a microspherical composite having a size of 0.5-1000 μm.

2. The pharmaceutical dosage form according to claim 1 further comprising a water soluble polymer entrapped in pores of said grains in an amount of 0.1-10% based on the weight of the grains.

3. The pharmaceutical dosage form according to claim 1, wherein said grains have a size of 1 to 300 μm.

4. The pharmaceutical dosage form according to claim 1, wherein said pores have an opening of 1 to 200 nm.

5. The pharmaceutical dosage form according to claim 1, wherein said grains have a specific surface area of 32 to 58 m^2 per unit gram.

6. The pharmaceutical dosage form according to claim 1, wherein said drug entrapped in said porous apatite grains is in an amount of 0.1-45% based on the weight of the grains.

7. The pharmaceutical dosage form according to claim 6, wherein said drug

entrapped in said porous apatite grains is in an amount of 1-30% based on the weight of the grains.

8. The pharmaceutical dosage form according to claim 2, wherein said water soluble polymer is selected from the group consisting of chitosan, gelatin, agar, cellulose, chitin, starch, dextrin, cyclodextrin, polylactic acid, polyamino acid, polyethylene glycol, polyacrylates, hyaluronic acid, polyvinyl alcohol, povidone and mixture thereof.

9. The pharmaceutical dosage form according to claim 8, wherein said water soluble polymer is cellulose, polyethylene glycol, polyvinyl alcohol, or povidone.

10. The pharmaceutical dosage form according to claim 1, wherein said apatite grains have a Ca to P molar ratio of 1.1 to 2.1.

11. The pharmaceutical dosage form according to claim 10, wherein said apatite grains have a Ca to P molar ratio of 1.3 to 1.60.

12. The pharmaceutical dosage form according to claim 1, wherein said apatite grains contains carbonate in an amount of 0.1-40% based on the weight of the grains.

13. The pharmaceutical dosage form according to claim 12, wherein said apatite grains have a Ca to P molar ratio of 1.3 to 1.60.

14. The pharmaceutical dosage form according to claim 1, wherein said drug is a peptide, protein, enzyme, DNA, RNA, nutrient supplement agent, anti-inflammatory drug, anti-biotic drug, anti-histamine drug, anti-bacterial drug, anti-fungal drug, decongestant, anti-depressant, anti-psychotic drug, anti-viral drug, anti-

oncolytic drug, vaccine, anti-epileptic drug, anti-asthma drug, antioxidant or extract of herb.

15. The pharmaceutical dosage form according to claim 1, wherein said drug is selected from a group of zinc gluconate, copper gluconate, carbinoxzmine maleate, dextromethorphan hydrobromide, glyceryl guaiacolate, pseudoephedrine hydrochloride, triprolidrine hydrochloride, acetaminophen, aspirin, ibuprophen, dexibuprophen lysinate, naproxen, ketoprofen, lactam, quinolone, macrolide or salts thereof, loperamide, famotidine, ranitidine, cimetidine or salts thereof, ibersartan, captopril, lisinopril or salts thereof, nefzodone, buspirone or salts thereof, chlorpheniramine, astemizole, pseudoephedrine, medicon, aspirin, actirin, nidolin, ascorbic acid, hydrocortisone, 5-fluorouracil, cis-platin, paclitaxel, ampicilin, cefadroxil, clindamycin, neomycin, nystatin, polyphenol, hydroquinone, and retinal A.

16. The pharmaceutical dosage form according to claim 15, wherein said drug is zinc gluconate, copper gluconate, aspirin, ibuprophen or ascorbic acid.

18. The pharmaceutical dosage form according to claim 1, wherein said biocompatible polymer is in an amount of 0.5% to 30% based on the weight of the grains.

19. The pharmaceutical dosage form according to claim 1, wherein said biocompatible polymer is selected from the group consisting of polylactic acid, polyglycolic acid, poly(lactic-co-glycolic acid), polyanhydrates, polyethylene glycol, polyethylene oxide, polyacrylates, polymethacrylates, dextran, polysaccharides, hyaluronic acid, and mixture thereof.

20. The pharmaceutical dosage form according to claim 19, wherein said biocompatible polymer is polylactic acid, polyethylene glycol, or poly(lactic-co-glycolic acid).

72. The pharmaceutical dosage form according to claim 2, wherein said grains have a size of 1 to 300 μm; said pores have an opening of 1 to 200 nm, said grains have a specific surface area of 32 to 58 m^2 per unit gram, said drug entrapped in said porous apatite grains is in an amount of 1-30% based on the weight of the grains, wherein said water soluble polymer is cellulose, polyethylene glycol, polyvinyl alcohol, or povidone; and wherein said apatite grains have a Ca to P molar ratio of 1.3 to 1.60.

41.37 (c)(1)(ix) Evidence appendix

None

41.37 (c)(1)(x) Related proceedings appendix

None